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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,033	05/11/2001	Pierre Chambon	065691-0222	5081

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,033	CHAMBON ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-19,21-33,35-61,65 and 66* is/are pending in the application.

4a) Of the above claim(s) *9,13,15-18,21,22,24-32,35-49,51 and 53-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10-12,14,19,23,33,50,52,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-19, 21-33, 35-61, 65 and 66 are pending in the application. Claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 4-8, 10-12, 14, 19, 23, 33, 50, 52, 65 and 66 are currently under examination.

This Office Action is in response to the Amendment filed on 1/18/05.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/18/05 has been entered.

Response to Amendment

The rejection of claims 33, 50 and 52 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1, 4-8, 10-12, 14, 19, 23, 33, 50 and 52 under 35 U.S.C.112 1st paragraph (scope of enablement) is maintained for reasons set forth of the record mailed on 6/16/04 and further discussed below. Newly added claims 65 and 66 are rejected for same reasons.

The rejection of claims 1, 4-8, 10, 11, 12, 14, 19, 23, 33 and 52 under 35 U.S.C.103 (a) is maintained for reasons set forth of the record mailed on 6/16/04 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10-12, 14, 19, 23, 33, 50, 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising in its genome a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits a specific transgene dependent phenotype, for example, increased glucose level and decreased triglyceride level when both copies of RXRα alleles are disrupted, as compared to mouse having RXRα expression, does not reasonably provide enablement for any transgenic mouse comprising a cell comprising claimed transgenes. Further, the specification does not enable any transgenic mouse without any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicants argue that all of the mice of the present invention have a predictable primary phenotype which allows one of skilled in the art to detect such mice and distinguish them from wild type mice as to investigate secondary phenotypes that are caused by the primary induced genetic lesion. Applicants assert that a phenotype is a visible observable or detectable characteristic of an organism resulting from an interaction of its genotype with the

environment, wherein the primary phenotype of the claimed mouse is the result of interaction of the genotype of the mice, and their treatment by synthetic anti-estrogens. Furthermore, Applicants argue that the working examples in the specification describe a method for observing/detecting the primary phenotype resulting from synthetic estrogen treatment. Moreover, Applicants argue that the specification also teaches keratinocyte selective ablation of RXRα and SNF2β, and Li et al., Imai et al., Weber et al., Chapellier et al., Imai et al. and the Declaration by Chambon provide additional examples of the claimed system of selective ablation in other tissues. Applicants thus conclude that the claimed invention is enabled to its full scope.

The above arguments have been fully considered but deemed unpersuasive. The reasons for non-enablement of the claimed invention were discussed in detail in the previous office action mailed on 6/16/04. In response to Applicants' argument with regard to phenotype, Applicants are reminded that the claimed invention does not recite any phenotype (either primary or secondary) according to Applicants' own definition. The claims do not recite any visible observable or detectable characteristic of the claimed mice other than their genotype. Knocking out/ablation of a gene itself is not considered as a phenotype because it is a description of the genetic structure. As such, for reasons discussed in the previous office action, the claims are not enabled because the essential elements of the claimed invention, phenotypes of the claimed mice, are not recited in the claims. Applicants are also reminded that the specification only discloses a transgenic mice comprising a transgene encoding the claimed fusion protein, but not mice comprising the fusion protein in any other manner. Moreover, the specification does not teach the claimed mouse having phenotype of altered metabolism in adipocytes or that resembles of diabetes as recited in claim 50, but only increased glucose level and decreased triglyceride level.

Absent evidence from the contrary, the claims are not enabled to their full scope. In addition, claim 33 recites "crossing said fertile adult mouse with a mouse in which at least one of the cell expresses said fusion protein." in step d). The specification only discloses crossing the transgenic mouse having recombination sites with another transgenic mouse expresses the fusion protein, but not any other mouse simply expresses the fusion protein in one or more cells. The prior art does not teach a mouse generated by such method either. Consequently, the claimed mouse is enabled only when it is obtained by such a method wherein the final product is generated by crossing two transgenic mouse. Therefore, this rejection is maintained. The Chambon Declaration and the references of Li et al., Imai et al., Weber et al., Chapellier et al., Imai et al have been considered. The examiner wants to clarify that this rejection is not necessarily limiting the claimed mouse to the specific phenotype of increased glucose level and decreased triglyceride level when both copies of RXRα alleles are disrupted, it is an example for acceptable phenotype. Applicants are welcome to amend the claims to recite phenotype(s) of the claimed mice that are commensurate with the scope of the claims.

Newly added claims 65 and 66 are rejected for same reasons as set forth in the previous office action and above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 8, 10, 11, 19 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al.

In response to this rejection, Applicants argue that the teaching of Feil lack expectation of success for achieving a system that works with 100% efficiency. Applicants also submit a declaration that reiterates the claimed invention is the first system that achieves 100% efficiency. Applicants further argue that extraordinary skill is required to obtain the present invention based on the teaching of Feil because Applicants are the first to obtain the claimed invention four years after the Feil publication. Applicants thus conclude that the claimed invention is not obvious.

This argument has been fully considered but deemed unpersuasive. The reasons for obviousness of the claimed invention in view of the prior art were discussed in detail in the previous office action. In response to the argument of the prior art does not teach 100% efficiency, Applicants are reminded that the alleged 100% deletion efficiency or tight temporal control of the generation of cell type/tissue-specific somatic mutation with 100% efficiency are not limitations of any of the pending claims. The claims are drawn to a mouse having in its genome the claimed fusion protein and gene or intergenic sequences flanked by recombinant sites recognizable by Cre, wherein said DNA sequences can be inactivated. The declaration has also been fully considered. Similarly, it does not overcome this rejection because the claimed invention does not have limitation for achieving 100% efficiency. As such, the prior art does not need to teach such inactivation have to be 100% to render the claimed mice obvious. The teaching of Feil thus gives reasonable expectation of success to make the claimed invention. In response to Applicants' argument that extraordinary skill is required to make the claimed invention, Applicants are reminded that the fact the invention is not made sooner does not

necessarily mean that extraordinary skill is required to achieve the claimed invention. Even the invention is obvious and there is motivation to make the invention, the ordinary artisan does not have to reduce it to practice in short amount of time. As Applicants are full aware that genetic manipulation of the mouse genome using the ES technology involves processes including making of the gene targeting construct, introduction of the construct to the ES cell and in vitro selection, blastocyst injection, implantation and successive mating of the chimeric mouse and transgenic mouse to obtain a homogenous background such that meaningful analysis can be done. The process of obtaining the final product takes considerable amount of time, and four years is not an unusually long time which necessary mean that extraordinary skill is required. As such, absent evidence from the contrary, the claims are obvious in view of the teaching of Feil, and this rejection is maintained.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Schwenk et al.

In response to this rejection, Applicants argue for same reasons as discussed above. Applicants further assert that Schwenk does not cure such deficiency. Applicants thus conclude that the claimed invention is not obvious in view of the combined teaching of Feil and Schwenk.

This argument has been fully considered but deemed unpersuasive. The reasons for obviousness of the claimed invention were discussed in detail in the office action mailed on 6/16/04. The Feil reference is not deficient for alleged lack of expectation of success for reasons given above. This rejection is thus maintained.

Claims 7, 12, 14, 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Indra et al., Ross et al. and Tontonoz et al. (1997, PNAS, Vol.94, pp.237-241)

In response to this rejection, Applicants argue for same reasons as discussed above. Applicants further assert that Indra, Ross and Tontonoz do not cure such deficiency. Applicants thus conclude that the claimed invention is not obvious in view of the combined teaching of Feil and Indra, Ross and Tontonoz.

This argument has been fully considered but deemed unpersuasive. The reasons for obviousness of the claimed invention were discussed in detail in the office action mailed on 6/16/04. The Feil reference is not deficient for alleged lack of expectation of success for reasons given above. This rejection is thus maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER